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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/855,587 | 05/16/2001 | Yoshiki Sasai | 766.44 | 1416 |

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FITZPATRICK CELLA HARPER & SCINTO
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

EXAMINER

TON, THAIAN N

ART UNIT PAPER NUMBER

1632

DATE MAILED: 10/07/2003

22

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/855,587

Applicant(s)

SASAI ET AL.

Examiner

Thái-An N. Ton

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 July 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,12-24,26,27,56 and 57 is/are pending in the application.
- 4a) Of the above claim(s) 21,56 and 57 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,12-20,22-24,26 and 27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 January 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 1620 6) ☐ Other: _____

DETAILED ACTION

Applicants' Amendment, filed 7/21/03, Paper No. 19, has been entered. Claims 3-11, 25 and 28-55 and 58-71 have been cancelled. Claims 1, 2, 12-24, 26, 27, 56 and 57 are pending. Claims 21, 56 and 57 are withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group(s), there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13. Claims 1, 2, 12-20, 22-25, 26 and 27 are under current examination.

Any rejection made of record in the prior Office action, mailed 1/16/03, Paper No. 14, and not made of record in the instant Office action, has been withdrawn in view of Applicants' arguments and/or amendments to the claims.

Priority

Certified copies of the Japan 2000-144059 and Japan 2000-298019 applications are proper and have been entered.

The translation of U.S. 60/257,049 has been received and considered.

Drawings

Applicants' formal drawings, filed 1/9/03, Paper No. 15 are approved by the Examiner.

Information Disclosure Statement

The Information Disclosure Statement filed 3/24/03, Paper No. 16, has been considered.

Claim Rejections - 35 USC § 112

Applicants' Notice regarding the deposit of FERM BP-7573 is has been made of record and has been accepted by the Examiner.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 1, 2, 12-20, 22-25, 26 and 27 under 35 U.S.C. 112, first paragraph, is withdrawn and a new rejection appears below.

Claims 1, 2, 12-20, 22-25, 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for inducing differentiation of an embryonic stem cell into an ectodermal cell which comprises co-culturing the ES cell under non-aggregation conditions with OP9, PA6 or NIH3T3 cells, wherein the culturing is carried out in the absence of retinoic acid, does not reasonably provide enablement for methods for inducing differentiation of an embryonic stem cell into an ectodermal cell by culturing the cell under non-

aggregation conditions in the absence of retinoic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly directed to methods for inducing differentiation of an ES cell into an ectodermal cells comprising culturing the embryonic stem cell under non-aggregation conditions, wherein culturing is carried out in the absence of retinoic acid.

The specification teaches that ES cells can be induced to differentiate under non-aggregating conditions when cultured in the presence of a stroma cell or a stroma cell-derived factor. See p. 38, lines 6-11. When culturing ES cells in the presence of a stroma cell, the cells do not form an embryoid body and the cell suspension is cultured under such conditions that the individual cells are present without mutual contact in the culturing system. The specification particularly teaches the differentiation of ES cells into a dopaminergic neuron by coculturing an ES cell [EB5] with a stroma cell, PA6, or with mouse fetal fibroblasts [MEFs]. It was found that after eight days of coculturing, the cells were fixed and analyzed immuologically using NCAM, a neuron marker, and a neuron specific marker, anti-anti-tubulin]. It was found 90% of the cells strongly expressed NCAM and postivie with the anti-tubulin antibody. See Example 1. The specification teaches the differentiation of embryonic stem cells into non-neuroectodermal cells by culturing

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the ES cell, EB5 with PA6 cells using BMP-4 serum-free medium and the resulting cells analyzed by anti-NCAM, anti-nestin or anti-E-cadherin. It was found that when medium without BMP-4 was used, the ES cell derived colonies were anti-NCAM negative, anti-nestin negative, and E-cadherin positive. See Example 2. ES cells, EB5 were cocultured with PA6, MEF, STO, NIH/3T3, OP9, CHO, MDCK, 3Y1 and COS cells for 8 days and then immunologically stained with the anti-NCAM antibody, and the ratio of positive colonies examined. It was found that the PA6, OP9 and NIH3T3 cells showed 95%, 45% and 10% respectively, whereas the other cells did not show significant nerve differentiation-inducing activities. See Example 3.

The claims as broadly written are not enabling because they do not require the presence of a stroma cell for co-culturing with the embryonic stem cell. The specification clearly teaches that as an alternative to directing differentiation by formation of an embryoid body, ES cells can be cultured in the presence of stroma cells. The working examples of the specification clearly support this, as they show that culturing on the stroma cell PA6 consistently produces cells which express neuronal markers. Furthermore, the specification fails to enable the directed differentiation of ES cells to ectodermal cells by co-culturing with any type of stroma cell, for the breadth claimed, as culturing with certain cell types [e.g., CHO, MDCK, COS cells] fails to produce cells that express NCAM. See Example 4.

Furthermore, the state of the art of directed differentiation of ES cells is unpredictable. Schuldiner *et al.* [PNAS, 97 :11307-11312, 2000] teach that differentiation of human ES cells were tested by addition of eight growth factors. Each growth factor was found to have a unique effect on differentiation, however, none of the growth factors was found to differentiate the cells into one cell type exclusively. See Abstract and Figure 4. Schuldiner teach that several soluble factors were shown to direct differentiation of mouse ES cells, for example, retinoic acid induces neuron formation, but none of the factors specifically directed differentiation of only one cell type in human ES cells. See p. 11307, col. 1-2, bridging ¶. Furthermore, Schuldiner teach that, "Whereas conditions that direct differentiation of mouse ES cells into neuronal, hematopoietic or cardiac cells have been published, a broad analysis of effects of various growth factors has not been performed." See p. 11310, 1st column, 1st full ¶. Accordingly, the state of the art clearly is unpredictable with regard to particular culturing conditions and/or factors which directly differentiate ES cells to a particular cell type.

Accordingly, in view of the lack of teaching or guidance provided by the specification with regard to inducing differentiation of an ES cell into an ectodermal cell without co-culturing with stroma cells, the unpredictable and undeveloped state of the art of directed differentiation of ES cells, it would have required undue experimentation for one of skill in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejection of claims 1, 2, 14, 24, 26 and 27 under 35 U.S.C. 102(b) as being anticipated by van Inzen [*Biochim et Biophys Acta* (1996) 1312:21-26] is withdrawn in view of Applicants' amendment to the claims.

The prior rejection of claims 1, 2, 12-15, 25-27 under 35 U.S.C. 102(b) as being anticipated by Kalyani *et al.* [*The Journal of Neuroscience* (1998) 18:7856-7868] is withdrawn in view of Applicants' amendments to the claims.

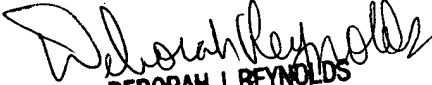
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Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)-872-9306.

TNT
Thái-An N. Ton
Patent Examiner
Group 1632


DEBORAH J. REYNOLDS
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600